REMARKS AND RESPONSE TO FINAL OFFICE ACTION

Preliminary Note

Applicants thank the Examiner for consideration of the arguments of record, and the withdrawal of prior rejections as noted on page 3 of the Final Office action, mailed August 25, 2005. Claims 1-5, 9-14, 16-21 and 23 are pending. By this amendment claims 7, 8, 24 and 25 are canceled; claims 1, 2, 5, 21 are amended to more closely parallel the claims recently granted in the corresponding European application and claim 17 is amended to provide proper antecedent basis. Subject matter of claims 24 and 25 can be found incorporated in amended claims 1 and 2. Support for the amendments can be found in the application as filed, for example at paragraphs 6, 33-37, 95, 102 and the original claims, *e.g.*, claim 5. The amendments do not constitute new matter. Applicants respectfully request that the Examiner reconsider the application in light of the remarks and amendments contained herein. The amendments merely provide clarity and conciseness to the claims, are not made for reasons relating to any cited references or asserted prior art. The amendments are not intended to be limiting the full scope of the invention as defined by the claims.

Rejection of Claims

Election/Restriction

By this amendment, claims 7 and 8 withdrawn in accordance with an election/restriction are formally cancelled. Applicants respectfully request that the Examiner acknowledge compliance.

"Double-Patenting" Rejection

At page 3, the Office Action maintains a double patenting rejection based on an allegation of "conflicting claims." Applicants respectfully traverse this rejection.[1] "Conflicting claims" are deemed as co-extensive in scope. (See MPEP 804.02). Section 804.02 is specifically directed to Double Patenting. Applicants acknowledge that the original rejection referenced 37 C.F.R. 1.78(b) invoking a

[1] Page 3 of the Office Action sports a section "***Rejections Maintained***" with a subheading "***Double Patenting***". In the second paragraph of this section, last sentence, The Action states: "This is not a double patenting issue [rejection?] but a conflicting claims issue involving multiple prosecutions of similar applications." Since the "issue" is not a common rejection, Applicants request guidance of whether this is a petitionable issue or an issue that should be appealed should further prosecution be advisable.

McDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 South Wacker Drive, 32nd Floor
Chicago, IL 60606

"conflicting claims" issue. Applicants respectfully assert that this rejection is improper for several reasons. First, the term "conflicting claims" when used in a sense consistent with the MPEP § 804.02 does not apply when claims are not co-extensive in scope. Since the claims cited in the Office Action are not co-extensive in scope, this rejection is improper according to the cited rule. Secondly, the Board of Patent Appeals and Interferences of the USPTO has provided guidance as to when two patents claim the same invention. The Board has taken a restrictive view of "same invention" (Rule 601(n)) requiring a two-way analysis to determine obviousness. Thus a single element in one claim not matched in another claim is sufficient basis for finding that the inventions are distinct (not the same). See, e.g., *Lilly v. Washington,* 334 F.3d 1264, CAFC 2003. For any or all of the above reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

I. Provisional Rejections for Non-statutory Double Patenting.

Applicants grateful acknowledge the Examiner's indication that a double patenting rejection may be seen in the future. Applicants however note that no (non-provisional) rejection is yet of record.

In a previous response Applicants stated:

> The Examiner rejected claims 1-6 and 9-23, stating that they conflict with the claims of Application Nos. 10/076,631 and 10/076,632. The Applicants disagree that there is any conflict, but for the present merely note that the rejection is a provisional one, as no patents have issued from any of the applications in question.

The Examiner responded however, stating:

> No indication of allowable subject matter will be made until such time as Applicants distinguish the inventions or file an appropriate disclaimer.

Applicants respectfully request that this reservation be withdrawn. The conflicting claims issue rejection has been shown to not apply to the circumstances of this application. Furthermore it is the claims that must be compared to determine the propriety of a double patenting rejection. Until claims are in desired final form, it is not possible to say whether a double patenting rejection is appropriate or to argue whether a rejection is improper. The MPEP acknowledges this circumstance in § 804 B.2:

> If a "provisional" statutory double patenting rejection is the only rejection remaining in both applications, the examiner should withdraw that rejection in the application with the earlier filing date and permit that application to issue as a patent. If both applications were filed on the same day, the applicant should be given an opportunity to elect which of the two should be allowed. In either situation, the examiner should maintain the double patenting rejection in the other application as a

"provisional" double patenting rejection, which will be converted into a double patenting rejection when one application issues as a patent.

Applicants respectfully assert that this instruction is applicable in the present application.

Without commenting on the propriety of the asserted provisional non-statutory double patenting rejection, Applicants will consider filing a terminal disclaimer, or amending the allegedly conflicting co-pending claims, once the statutory bases for rejection are resolved.

II. Rejection of Claims under 35 U.S.C. § 112, first paragraph.

A. Written Description.

Claims 1-6, 9-14, 16-21, and 23-25 stand rejected under 35 U.S.C. § 112, first paragraph for allegedly containing subject matter which was not described in the specification such that it reasonably conveys to one of skill in the art that the inventors had possession of the claimed invention as of the filing date. Claims 24 and 25 are cancelled. With respect to claim 1, Applicants note that the claim does not recite "S"; thus the rejection as relates to "S" does not apply to claim 1 or claims directly depending therefrom that do not recite "S". With respect to remaining claims at issue Applicants respectfully disagree for the following reasons.

In order to satisfy the written description requirement, "a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." MPEP § 2163. Further, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was 'ready for patenting' such as...by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention." Id.

The rejection focuses on definitions used to describe the claimed nucleic acid, in particular the terms "S" and "F". Applicants' description of these terms is of record. The specification describes "S" at, for example, paragraphs [0023], [0036], [0061], Examples 1-3, and Example 10. As noted in prior communications, and by the Examiner, Applicants have clearly described in the specification that the signal sequence "S" can be used to optimize/increase fusion protein yields. Nevertheless, the increased yield is not necessarily accomplished by merely expressing and generating more target protein, but, for example, through secretion of the target protein to the extracellular matrix and/or

eliminating the need to reconstitute, refold, and/or renature the target protein. This is described in the specification, for example, at paragraphs [0005-0006], which detail how typical protein yields decrease when the target protein is purified from inclusion bodies and/or requires refolding after initial separation steps. Thus, including the "S" signal sequence increases yield by, for example, allowing for increased/optimized export compatibility through inner bacterial membranes and/or allowing the target protein to adopt its proper 3-dimensional conformation (*i.e.*, properly folded). The particular signal sequences "S" recited in the disclosure are merely examples of signal sequences that can increase protein yields, such as by increasing secretion from the cell and eliminating the need to refold or renature the target protein, as described in the specification. Given these arguments Applicants have nevertheless elected to amend Claim 2 as noted above to even more clearly describe the invention in an effort to move prosecution of the application forward.

Thus, Applicants respectfully assert that the full scope of the term "S" as used in the claims is properly supported by the written description found in the specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

"F" or hirudin: secretion of protein encoded by "Y"

The term "F" is described throughout the specification, for example in paragraphs [0008], [0026], [0032], [0050], [0062], and Examples 1-3. The particular Examples teach nucleic acids that comprise hirudin variants that allow for secretion of the expressed amino acid sequence from the cell. In addition, the specification at paragraph [0006] describes (a) international patent application PCT/EP00/08537 which discloses the bacterial expression and export of lepirudin using specific signal sequences; and (b) German Application No: 100 33 195.2 which describes the expression and export of a bifunctional protein composed of hirudin and factor Xa inhibitor.

The Office Action at page 5, lines 7-10 alleges that "hirudin or its derivatives or variants have not been shown to have this property [allow secretion of a protein encoded by Y into a fermentation medium]." Applicants respectfully direct the Examiner's attention to the specification, for example, at paragraph 25: "For instance the present invention may involve DNA sequences coding for hirudin or a derivative thereof (F) and proinsulin or a derivative thereof (Y)"; and paragraph 35: "The nucleic acid sequence F may encode for lepirudin, Ser-hirudin or Ala-hirudin". The specification here and elsewhere clearly teaches hirudin or a derivative thereof as "F". Thus the skilled artisan upon reading

the present specification would understand that the present inventors would have been in possession of the invention with hirudin or a derivative thereof as of the filing date.

The Office Action states:

> A signal sequence "S" allows for secretion of a protein into a fermentation medium. Every single Example of the specification and the art from which the plasmids were derived, have signal sequences. This specification fails to teach that hirudin or derivative thereof has the functional property of allowing secretion. There is no teaching in the specification that provides for an expression construct limited to hirudin or derivative thereof provides for secretion [sic]. In other words, hirudin or derivative thereof itself has not been demonstrated in any host cells to be recombinantly produced as a secreted product, absent more.

While "S" alone is functional in directing expressed peptide to the membrane for secretion, other components of the cell are necessary or effective to complete the task and proper function of the secreted protein is not guaranteed simply by the presence of "S". The effective function of hirudin and derivatives e.g., "allowing" secretion of functional expressed protein, is set forth in the present specification, for example, in paragraph 6:

> "[I]t was then surprisingly found that hirudin is exported with high yields not only as a fusion protein with TAP but also as part of a fusion protein with polypeptides such as proinsulin derivatives, that it is biologically active and that surprisingly a fusion partner such as proinsulin is present in the correct three-dimensional structure. This unexpected result leads to the possibility of more cost-effective production of, for example, insulin by bacterial host/vector systems, since the step of in vitro refolding after intracellular expression, which is associated with losses in yield which are not negligible, can be dispensed with and in this way a simpler protein purification process results. Another advantage is that chaotropic aids added to dissolve the fusion protein in traditional processes for the production of insulin in E. coli are not required. Ecologically, this leads to less environmental pollution by avoiding the corresponding waste."

Thus according to the teachings of the specification, incorporating hirudin as part of a fusion construct allows proinsulin harvest from extracellular space in a desired form ("exported with high yields . . . in the correct three-dimensional structure"). Yields are also improved by avoiding losses during *in vitro* folding. This additional evidence and description further demonstrates that the inventors were in possession of the present invention with "F" as hirudin or a derivative. Reconsideration and withdrawal of this aspect of the rejection are respectfully requested.

The Office Action at page 5 lines 19 and 20 states: "This is the issue here with the definition of 'F' in the specification." Perhaps the statement in the Office Action is based on a misreading of the verb "allow". ("In other words, hirudin or derivative thereof itself has not been demonstrated in any

host cells to be recombinantly produced as a secreted product, absent more.") Page 5, lines 15-17. This sentence is interpreted by Applicants to espouse a misunderstanding that "allow" as used here means "suffices" or "is sufficient all by itself" to effect secretion. Clearly since secretion involves many separate parts, e.g., from binding of polymerase to escaping from the extracellular surface of the cell, (including a part accomplished by "S") any one element or component cannot be expected to alone suffice to effect the entire process. The dictionary definition (*Webster's II New College Dictionary)* "to permit" is more apropos. Inclusion of the hirudin or derivative does not prevent and in fact facilitates secretion of *desired* peptide or protein. Thus with proper understanding of the definition of the verb "allow", no issue of indefiniteness relating to written description is present. Reconsideration and withdrawal of this aspect of the rejection are respectfully requested.

Given Applicants' disclosure those of skill in the art would understand the meaning of the term "F" as used in the claims and specification, and would understand that Applicants possessed the invention at the time of filing.

Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

B. Enablement.

Claims 1-6, 9-14, 16-21, and 23-25 stand rejected under 35 U.S.C. § 112, first paragraph because the specification, allegedly, does not reasonably provide enablement for the claimed nucleic acids encoding fusion proteins, plasmids, host cells, and methods of making and purification. Claims 24 and 25 are cancelled. Applicants respectfully disagree with this rejection for the following reasons.

In order for claims to be enabled, the specification must disclose at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim. Applicants are not required to disclose other or all methods by which the claimed invention can be made. MPEP § 2164.01(b). According to MPEP § 2164.02, "[c]ompliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether an example is disclosed." Further, "[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904,908, 614 USPQ 642, 645 (CCPA 1956)."

The Examiner has acknowledged that certain aspects of the claims are enabled. Nevertheless, objection is made regarding the asserted lack of working Examples that demonstrate the nucleic acid of Claim 1 (*i.e.*, a nucleic acid that can lack a promoter and signal sequence) is able to direct secretion of the translated amino acid sequence out of the host cell.

Applicants have provided ample guidance in the specification, including 10 working Examples describing certain embodiments of the invention, that provide one of skill more than adequate guidance to make and use the full scope of the invention, as claimed. As disclosed in the specification at paragraphs [0023-0037], F is a DNA sequence coding for an amino acid sequence which allows secretion of a protein encoded by Y into a fermentation medium, and S is a DNA sequence coding for a signal sequence allowing optimal yields. The MPEP clearly states that there is no statutory provision that requires an Applicant to disclose working Examples that detail the full scope of the claimed invention, so long as one skilled in the art can practice it without undue experimentation. Applicants have provided a detailed description of the invention and in particular certain embodiments of the invention as described in Examples 1-10. This disclosure more than adequately describes to one of skill in the art how to make and use the full scope of the claimed invention without undue experimentation. It is well settled that some experimentation is allowable, so long as it is not undue. *See*, M.P.E.P. § 2164.06; and *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

At page 5, lines 20–23, the Office Action further states: "Further the specification does not define hirudin derivatives and therefore provides for unlimited variation of hirudin. The exemplification of two known N-terminal substitutions and lepirudin in the Examples does not provide adequate written description of a genus of unlimited variation." Applicants respectfully traverse this aspect of the present rejection. Applicants respectfully direct the Examiner's attention to the specification, for example at paragraph 8.

> The invention includes the use of hirudin and hirudin variants for the formation of fusion proteins, for example with simian proinsulin or derivatives thereof. Particular aspects of the invention use one of the natural hirudin isoforms (the natural isoforms together are denoted "hirudin"). Natural isoforms are, for example, Val-Val-hirudin or Ile-Thr-hirudin. Other aspects of the invention use a variant of a natural hirudin isoform. A hirudin variant is derived from a natural hirudin isoform but contains, for example, additional amino acids and/or amino acid deletions and/or amino acid exchanges compared with the natural isoform. A hirudin variant may contain alternating peptide segments of natural hirudin isoforms and new amino acids. Hirudin variants are known and are described, for example, in DE 3 430 556. Hirudin variants are commercially

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive, 32nd Floor
Chicago, IL 60606

available in the form of proteins (Calbiochem.RTM. Biochemicals, Cat. No. 377-853, -950-960). The hirudin variant sequences are at least 40% homologous to lepirudin, such that 40% of the total amount of the 65 amino acids known from lepirudin should be found within the variant. The hirudin variant sequences may be even more homologous, such as at least about 60%, or at least about 80%, homologous to hirudin. The % homology is calculated by the Compare Program which is available from the Wisconsin Package distributed by the Genetics Computer Group; 575 Science Drive; Madison, Wis.

Thus no "genus of unlimited variation" is implicated. Reconsideration and withdrawal of this aspect of the rejection are respectfully requested.

Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

III. Rejection of Claims under 35 U.S.C. § 112, second paragraph.

Claims 1-5, 9-14, 16-21, and 23-25 stand rejected under 35 U.S.C. § 112, second paragraph for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More specifically, objection is made to Claim 3, Claim 4, Claim 17, and the use of the term "signal sequence" throughout the claims. Applicants respectfully disagree for the following reasons.

As recited in MPEP § 2173.02, "[t]he essential inquiry pertaining to [the requirement for definiteness of 35 U.S.C. § 112] is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of: (A) The content of the particular application disclosure; (B) The teachings of the prior art; and (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made."

As to claim 3, the Examiner objected that the phrases "smompa derived from," "ecoompc derived from," "af009352 derived from," "aeoynxa derived from," are "not described nor specifically defined in the specification." The Applicants respectfully disagree. The sequence represented by "smompa" is defined at paragraph 128 as a "[s]ignal sequence smompa derived from the ompA gene for major outer membrane protein of Serratia marcescens (GenEMBL data base locus: SMOMPA, 1364 bp DNA BCT Mar. 30, 1995)." The sequence represented by "ecoompc" is similarly defined at paragraph 129; "af009352" at paragraph 130; and "aeoynxa" at paragraph 131. The Office Action states: "Limitations of specific sequences of particular database genes are not read into the claims."

Applicants respectfully agree that such is the intent. The references to elements in databases are not intended to limit claim scope. The words (acronyms) are intended to define the claims. E.g., "Signal sequence ecoompc derived from E. coli ompC gene coding for major outer membrane protein." Paragraph 129. While additional guidance by way of example is provided by reference to e.g., Gen EMBL content, to assist the skilled or unskilled artisan in understanding the defined gene and its signal sequence, the skilled artisan would have alternative means to access sequence information, including corrections or alternative sequence information associated with the identified genes that are maintained in such databases. The word (acronym) definitions enable anyone of ordinary skill in the art to make and use the sequences in a manner fully commensurate with the scope of the claims. Reconsideration and withdrawal of this rejection are respectfully requested.

As to claim 4, the Examiner objected that "Ser-hirudin" and "Ala-hirudin" "have no meaningful interpretation." But these derivatives are known and readily available from commercial suppliers, as the specification points out. Hirudin variants with changes in the N-terminus are named according the conventions known in the art and described in, e.g., European Patent Application No. 86117098.3 (see, page 1, paragraph 2, sentence beginning at the end of the sixth line of the second paragraph.) Thus one or more amino acids listed before a named peptide or protein (unless otherwise described, e.g., by an identifying number or other descriptive text) is taken as the N-terminal amino acid (or acids). Hence, "Ser-hirudin" and "Ala-hirudin" are hirudins with an N-terminal "Ser" and "Ala," respectively, instead of the "Val-Val" and "Ile-Thr" N-terminus of the hirudin variants exemplified in the European application. See, e.g., present application as published, paragraphs 95 and 102.

With respect to the misunderstanding of claim 4 "to encompass any substitution, insertion or deletion in variation" Applicants believe that the discussion relating to written description above should obviate this aspect of the rejection. Accordingly, reconsideration and withdrawal of this aspect of the rejection are respectfully requested.

As to claim 17, the amendment in form is believed to obviate this rejection.

Further argument is made that Applicants use of the term "signal sequence" is contrary to the common definition of that term as understood by those of skill in the art. Specific reference to the nature of signal sequence, S, is made throughout the specification, as noted above in Section II (A). Given the disclosure in the specification (*e.g.*, paragraphs [0023], [0036], [0061], Examples 1-3, and Example 10) and the instant amendments to the claims, the skilled artisan can easily ascertain the

meaning of signal sequence, S, as used in the claims. Applicants respectfully request reconsideration and withdrawal of this basis of rejection.

New Grounds for Rejection of Claims under 35 U.S.C. § 112, second paragraph.

Claims 1-5, 9-14, 16-21, and 23-25 stand newly rejected under 35 U.S.C. § 112, second paragraph for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In light of the amendments to the claims, Applicants respectfully disagree for the following reasons.

Claims 1 and 24, and the claims that are dependent thereon, stand rejected for use of the term hirudin derivative. In light of the above amendments to the claims, Applicants believe that this rejection has been obviated. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 14 and 21, and the claims that are dependent thereon, stand rejected for recitation of terms including "fermentation supernatant," "fermentation medium," and "produced thereby." The claims have been amended as noted above, which Applicants believe to obviate the rejections based on the terms "fermentation medium" and "produced thereby." As to the term "fermentation supernatant" Applicants submit that the terms "supernatant," "broth," and "medium" (and descriptive variations of those terms) are used interchangeably in the specification, the difference between a broth or medium and a proper "supernatant" only requiring settling of cells. Thus, the term "fermentation supernatant" properly describes the extracellular growth medium used to culture the host cells during fermentation, as cellular proteins and components (products of fermentation) are being excreted from the host cells into the culture medium, making the broth or medium a "fermentation supernatant." Nevertheless, Applicants have amended the claims in order to clarify the language and expedite prosecution. However, Applicants respectfully contend that one of skill in the art would plainly understand the meaning of these terms especially from the context in which they are used in the specification. The specification and particularly the Examples make clear when host cells are separated from liquid medium, whether the term used to describe the liquid medium is "broth," "medium," "supernatant" or any variant thereof. Accordingly, Applicants respectfully request reconsideration and withdrawal of this basis of rejection.

IV. Rejection of Claims under 35 U.S.C. § 102(b).

At page 10, the Office Action rejected claims 1, 2, 6, 9-15, 17, 22 and 23 as allegedly being anticipated by Dawson, Examples 1-15. Applicants respectfully traverse this rejection. Applicants note that claim 15 is not currently pending in the present application. Comments below are not intended to apply to the canceled claim.

According to MPEP § 2131, "'[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.' *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). 'The identical invention must be shown in as complete detail as is contained in the...claim.' *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)."

The pending claims are not anticipated by the disclosure of Dawson, as Dawson fails to teach or disclose a nucleic acid comprising a sequence coding for a fusion protein comprising a hirudin, 0-10 codons, 0-1 arginine codon, and a sequence coding for proinsulin or insulin. Therefore, Dawson also fails to teach or disclose that same nucleic acid sequence further comprising a promoter, a signal sequence, and an untranslated expression enhancing sequence. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

VI. CONCLUSION

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. Allowance of the claims is thereby respectfully solicited. The Examiner is invited to contact the undersigned representative by telephone at 312-913-0001 to discuss any aspect of this response.

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff LLP

Dated: February 27, 2006

By: _____
Christopher P. Singer
Registration No. 48,701

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive, 32nd Floor
Chicago, IL 60606